

## Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio

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- 1 Statins inhibit synthesis of mevalonate, a precursor of ubiquinone that is a central compound of the mitochondrial respiratory chain. The main adverse effect of statins is a toxic myopathy possibly related to mitochondrial dysfunction.
- 2 This study was designed to evaluate the effect of lipid-lowering drugs on ubiquinone (coenzyme Q10) serum level and on mitochondrial function assessed by blood lactate/pyruvate ratio.
- 3 Eighty hypercholesterolaemic patients (40 treated by statins, 20 treated by fibrates, and 20 untreated patients, all 80 having total cholesterol levels  $>6.0 \text{ mmol l}^{-1}$ ) and 20 healthy controls were included. Ubiquinone serum level and blood lactate/pyruvate ratio used as a test for mitochondrial dysfunction were evaluated in all subjects.
- 4 Lactate/pyruvate ratios were significantly higher in patients treated by statins than in untreated hypercholesterolaemic patients or in healthy controls ( $P < 0.05$  and  $P < 0.001$ ). The difference was not significant between fibrate-treated patients and untreated patients.
- 5 Ubiquinone serum levels were lower in statin-treated patients ( $0.75 \text{ mg l}^{-1} \pm 0.04$ ) than in untreated hypercholesterolaemic patients ( $0.95 \text{ mg l}^{-1} \pm 0.09$ ;  $P < 0.05$ ).
- 6 We conclude that statin therapy can be associated with high blood lactate/pyruvate ratio suggestive of mitochondrial dysfunction. It is uncertain to what extent low serum levels of ubiquinone could explain the mitochondrial dysfunction.

**Keywords** statins fibrates hypercholesterolaemia ubiquinone lactate mitochondria

### Introduction

Hydroxy-methylglutaryl (HMG)-CoA reductase inhibitors induce unselective inhibition of the common mevalonate pathway in liver and are one therapeutic class for the treatment of hypercholesterolaemia [1]. The therapeutic class includes lovastatin, simvastatin, pravastatin, and fluvastatin (statins). The main clinical adverse effects of statins are muscular and include elevation of serum creatine kinase, sometimes associated with myalgia, rhabdomyolysis, and rarely, cases of

inflammatory myopathies [2–5]. The pathogenesis of statin-induced muscle involvement is still unclear [6, 7]. Patients treated by the combination of statin and fibrate therapy have been considered at particular risk for myopathy and rhabdomyolysis [8]. Single case studies have suggested the hypothesis of a mitochondrial dysfunction at the origin of statin- [9, 10] and fibrate-related myopathies [11].

Statins inhibit synthesis of mevalonate, a precursor of both cholesterol and ubiquinone. Some studies have documented a decrease of serum levels of ubiquinone in

patients receiving statins [12–15], and it is debated whether or not the decrease of ubiquinone level parallels that of cholesterol level [13, 15]. Ubiquinone (Coenzyme Q10) is a key-coenzyme of the mitochondrial respiratory chain [16], and a drug-induced decrease of ubiquinone production might therefore induce mitochondrial dysfunction [13].

Lactic acid is produced by reduction of pyruvate, a product of anaerobic metabolism of glucose, and oxidative metabolism of pyruvate proceeds partly through the mitochondrial respiratory chain. Dysfunction of the respiratory chain may lead to inadequate removal of lactate and pyruvate from the circulation and elevated lactate/pyruvate ratios are observed in mitochondrial cytopathies [17, 18]. Blood lactate/pyruvate ratio [19] is, therefore, widely used as a noninvasive test for detection of mitochondrial cytopathies [17, 18] and toxic mitochondrial myopathies [20].

To detect mitochondrial dysfunction in patients treated by statins or fibrates, we determined the blood lactate/pyruvate ratio [19] as done previously to investigate toxic mitochondrial myopathies [20]. We also evaluated serum levels of ubiquinone to answer the following questions: (1) is treatment by statins or fibrates associated with mitochondrial dysfunction? (2) is treatment with statins or fibrates associated with low serum levels of ubiquinone, and does the decrease of ubiquinone parallel that of cholesterol? and (3) is there a relationship between blood lactate/pyruvate ratio and ubiquinone serum levels?

## Methods

### Patients

Patients with hypercholesterolaemia were enrolled. Hypercholesterolaemia was defined as a serum level of total cholesterol above  $6.0 \text{ mmol l}^{-1}$ . Patients in whom lipid-lowering therapy had been modified in the previous 2 months and patients with high serum creatine kinase levels ( $>200 \text{ iu l}^{-1}$ ) or muscular symptoms were not included. Exclusion criteria were as follows: hepatic failure or elevated serum aminotransferase levels ( $\geq$  twofold), fever, recent surgery ( $<2$  weeks), recent traumatism or intense physical activity ( $<2$  weeks), treatment by biguanides, or recurrent cerebral ischaemic episodes. Group 1 included 40 consecutive hypercholesterolaemic subjects treated by statins: 23 men and 17 women, aged 21–76 years, median: 51, treated by simvastatin (28 patients), pravastatin (eight patients), or fluvastatin (four patients). Group 2 included 20 consecutive hypercholesterolaemic subjects treated by fibrates: 16 men and four women, aged 38–70 years, median: 54, treated by ciprofibrate (nine patients), fenofibrate (eight patients), or gemfibrozil (three patients). Group 3 included 20 consecutive hypercholesterolaemic subjects who did not receive any cholesterol-lowering drug: 12 men and eight women, aged 27–75 years, median: 46. A group of 20 subjects (11 men and nine women, aged 25–66 years, median: 35) without hypercholesterolaemia served as controls.

### Study design

All patients participating in the study had a clinical and neurological examination, including assessment of muscular strength. Blood lactate and pyruvate and serum levels of total and HDL cholesterol, triglycerides, ubiquinone, aspartate and alanine aminotransferase, and creatine kinase were assayed on the first day of the study. A second blood sample for lactate and pyruvate was obtained after 1 week.

The study was approved by the Ethics Committee of Henri Mondor Hospital and each patient gave informed consent.

### Lactate and pyruvate determinations

Blood samples were collected by direct venepuncture between 08.30 h and 10.00 h, after an overnight fast. The collected blood samples were immediately added to an equal volume of 1 M chilled perchloric acid. The solution was mixed vigorously and centrifuged at  $2000 \text{ g}$  for 10 min at  $4^\circ \text{ C}$ .

Lactate was measured in the supernatant with a Roche Model 640 Lactate Analyzer, specific for L-lactate (Roche, Basel, Switzerland). Pyruvate was measured in the supernatant with a kit (Boehringer, Mannheim, Germany). The optimized method depended on the oxidation of reduced nicotinamide-adenine dinucleotide in the presence of lactate dehydrogenase at an optimal pH of 7.0 [21], as described [19].

Reference values for lactate/pyruvate ratio were  $13.2 \pm 6.1$  (mean  $\pm 2$  s.d.s) [21]. We considered that a lactate/pyruvate ratio was normal if lower than 20. In all subjects, two evaluations of lactate and pyruvate were performed. Patients were considered to have a high lactate/pyruvate ratio if they had one or two abnormal evaluations ( $\geq 20$ ) [20]. Patients with two normal evaluations were considered to have normal lactate/pyruvate ratio.

### Ubiquinone determinations

Ubiquinone levels were determined in serum by high performance liquid chromatography (h.p.l.c.) adapted from Okamoto *et al.* [22, 23]. The analytical conditions for the determination of ubiquinone were as follows: stationary phase, C18–5 (5  $\mu\text{m}$  particles) column, stainless-steel,  $250 \times 4.6 \text{ mm}$ ; mobile phase: methanol-n hexane (75:25); flow rate:  $1 \text{ ml min}^{-1}$ ; range: 0.08; measuring wavelength: 275 nm. The h.p.l.c. measurements were performed at room temperature. Extraction was performed as follows: 0.4 ml plasma from heparinized venous blood were pipetted into a stoppered brown-glass tube and 0.3 ml distilled water and 7 ml of a mixture of ethanol/n-hexane (2:5) were added. The tube was then rapidly shaken for 10 min and centrifuged at  $500 \text{ g}$  for 10 min. This extraction procedure was repeated three times. The combined n-hexane phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 0.5 ml ethanol and an aliquot

**Table 1** Lactate/pyruvate ratio, ubiquinone serum level, and molar ratio ubiquinone/LDL cholesterol

Groups	Lactate/ pyruvate <sup>a,b</sup>	Ubiquinone <sup>c</sup> (mg l <sup>-1</sup> )	Ubiquinone/ LDL cholesterol <sup>d</sup> ( $\times 10^{-4}$ )
Statin-treated patients (n=40)	19.0 $\pm$ 0.8 <sup>e,f</sup>	0.75 $\pm$ 0.04 <sup>e</sup>	1.69 $\pm$ 0.07 <sup>f</sup>
Fibrate-treated patients (n=20)	18.0 $\pm$ 1.1 <sup>g</sup>	0.91 $\pm$ 0.09 <sup>h</sup>	2.31 $\pm$ 0.24
Untreated patients (n=20)	15.9 $\pm$ 0.7 <sup>h</sup>	0.95 $\pm$ 0.16 <sup>h</sup>	2.02 $\pm$ 0.17 <sup>h</sup>
Controls (n=20)	13.1 $\pm$ 0.6	0.69 $\pm$ 0.04	2.69 $\pm$ 0.20

<sup>a</sup>Lactate/pyruvate: blood lactate/pyruvate ratio; <sup>b</sup>analysis of variance (ANOVA):  $F=9.0$  ( $P<0.0001$ ) <sup>c</sup>3.9 ANOVA:  $F=9.0$ ,  $P<0.01$ , <sup>d</sup>8.1 ANOVA:  $F=P<0.0001$ )

Values indicated are means  $\pm$  s.e. mean. Differences were determined by analysis of variance, followed by Newman-Keuls' procedure for *post hoc* comparisons if the ANOVA showed a significant difference ( $P<0.05$ ) among groups. Differences were not significant unless stated.

<sup>a</sup>Blood lactate/pyruvate ratio. In all subjects, two evaluations of lactate and pyruvate were performed; the value considered in the analysis of data is the upper value.

<sup>e</sup> $P<0.05$  vs untreated patients

<sup>f</sup> $P<0.001$  vs controls

<sup>g</sup> $P<0.01$  vs controls

<sup>h</sup> $P<0.05$  vs controls

of 50  $\mu$ l of the ethanol solution was injected into the column.

The coefficient of variation, determined by processing six times independently the same serum sample, was 8.4%. Reference values for serum ubiquinone levels were obtained from 33 healthy adults (18 men and 15 women; aged 25–79 years, median: 38) and were  $0.65 \pm 0.40$  mg l<sup>-1</sup> (mean  $\pm$  2 s.d.s).

#### Cholesterol determinations

Cholesterol was measured enzymatically and HDL cholesterol was measured after precipitation of apolipoprotein B with dextran sulphate 500–MgCl<sub>2</sub> [24]. The LDL cholesterol was calculated by Friedewald formula [25].

The ratio plasma ubiquinone/LDL cholesterol was calculated to evaluate the independent effects of statins on cholesterol and ubiquinone metabolism.

#### Statistical analysis

Differences in biochemical data were determined by analysis of variance (ANOVA), followed by Newman-Keuls' procedure for *post hoc* comparisons if the ANOVA showed a significant difference ( $P<0.05$ ) among groups. The proportions of patients with high lactate/pyruvate ratios in the different groups were compared using Fisher's exact test. Determination of

the correlation coefficient ( $r$ ) was used for comparison of lactate/pyruvate ratio and ubiquinone level.

## Results

#### Lactate and pyruvate determinations

Results are presented Tables 1 and 2. Lactate/pyruvate ratios were significantly higher in statin-treated patients than in untreated hypercholesterolaemic patients ( $P<0.01$ ). A lactate/pyruvate ratio  $\geq 20$  was significantly more frequent in Group 1 (patients treated by statins) than in Group 3 (untreated patients) ( $P<0.02$ ) or in the control group ( $P<0.001$ ). No significant difference was found between Group 2 (patients treated by fibrates) and Group 3 or between Group 2 and the control

**Table 2** Patients with high blood lactate/pyruvate ratio

Lactate/pyruvate ratio	High	Normal
Statin-treated patients (n=40)	16	24
Fibrate-treated patients (n=20)	5	15
Untreated patients (n=20)	2	18
Controls (n=20)	0	20

In all subjects, two evaluations of lactate and pyruvate were performed. High L/P: patients with one or two abnormal evaluations ( $\geq 20$ ); normal L/P: patients with two normal evaluations.

group. There was no significant difference for lactate/pyruvate ratios among those receiving a statin, according to the administered compound (i.e. simvastatin, pravastatin, or fluvastatin).

#### *Ubiquinone determinations*

Results are presented Table 1. Ubiquinone serum concentrations were lower in Group 1 (patients treated by statins) than in Group 3 (untreated hypercholesterolaemic patients) ( $P < 0.05$ ). The difference was not significant when the molar ratios ubiquinone/LDL cholesterol were compared. The molar ratios ubiquinone/LDL cholesterol were significantly lower in Group 1 than in normocholesterolaemic controls ( $P < 0.01$ ). Ubiquinone serum level was significantly higher in Group 3 (untreated hypercholesterolaemic patients) than in normocholesterolaemic controls ( $P < 0.05$ ).

No correlation was found between age and plasma level of ubiquinone in the two groups of controls, namely the normal subjects and the untreated hypercholesterolaemic patients. No correlation was found between lactate/pyruvate ratio and serum ubiquinone level or between lactate/pyruvate ratio and the molar ratio ubiquinone/LDL cholesterol.

#### **Discussion**

In the present study, asymptomatic patients treated with statins, unlike those receiving fibrates, frequently had an increased blood lactate/pyruvate ratio and had lower ubiquinone serum levels than untreated patients. No correlation could be established between blood lactate/pyruvate ratio and ubiquinone serum concentration at the individual level. We also found higher serum ubiquinone levels in patients with untreated hypercholesterolaemia than in normocholesterolaemic subjects but there was no change in the ubiquinone/LDL cholesterol ratio. This result is in accordance with previous studies [26].

Since redox status assessed by blood lactate/pyruvate ratio may vary in a given individual and can be normal one day and abnormal another day in patients with proven mitochondrial dysfunction [20, 27], we repeated evaluation of lactate and pyruvate in all subjects. The finding of high blood lactate/pyruvate ratios in 16 of 40 patients receiving statins (40%) strongly supports the hypothesis of a mitochondrial dysfunction associated with statin therapy. In a previous study, we found high lactate/pyruvate ratios in all evaluated patients with zidovudine-induced mitochondrial myopathy [20]. The absence of muscular symptoms in the patients studied here may explain the lower percentage with high lactate/pyruvate ratios. The hypothesis of a mitochondrial dysfunction at the origin of muscular disorders due to statins had been previously suggested [9, 10, 28]. In an experimental animal myopathy induced by lovastatin, marked ultrastructural abnormalities were observed in mitochondria [29]. However, other investigators did

not find such abnormalities in a model of simvastatin-induced myopathy [30].

Fibrate therapy was associated with high lactate/pyruvate ratios in some cases. Reports on muscular syndromes related to fibrate therapy have mentioned mitochondrial abnormalities in muscle [11, 31]. The hypothesis of a mitochondrial dysfunction induced by fibrate therapy still needs to be substantiated. Elevated lactate/pyruvate ratios were also occasionally found in untreated hypercholesterolaemic patients, supporting the hypothesis that hypercholesterolaemia is itself associated with muscle damage [6].

The cause of mitochondrial dysfunction associated with statin therapy is unclear. The role of ubiquinone may be suspected, since treatment by statins, but not by fibrates was associated with low ubiquinone concentrations. Whether statins lower serum ubiquinone independently of LDL cholesterol lowering has been debated [13, 15, 26]. In this study, we found that the molar ratio ubiquinone/LDL cholesterol was significantly lower in patients treated with statins than in untreated patients, implying that the decrease of ubiquinone did not parallel the decrease of LDL cholesterol. The absence of correlation between blood lactate/pyruvate ratio and ubiquinone serum level at the individual level is puzzling. The relationship between serum ubiquinone and mitochondrial function is indeed unclear. The tissue biosynthesis of ubiquinone might not be reflected by its serum level [32] and discrepancy between very low muscular and normal circulating levels of ubiquinone has been observed in patients with mitochondrial cytopathies [33]. Cell culture studies failed to demonstrate any mitochondrial dysfunction in cells severely depleted in ubiquinone [34]. Moreover, most studies evaluating the effect of oral supplementation by ubiquinone in patients with mitochondrial cytopathies have yielded negative results [35]. It is still unknown whether supplementation with oral doses of ubiquinone in statin receivers having low serum levels of ubiquinone at the onset of therapy could prevent the occurrence of muscle disorders.

Mitochondrial dysfunction could also be explained by membrane damage induced by the inhibition of cholesterol and dolichol synthesis [13]. In an animal model of experimental lovastatin myopathy, the earliest changes involved the mitochondria and the sarcoplasmic reticulum [29]. In this hypothesis, mitochondrial dysfunction could be only one feature of a toxicity primarily affecting membranous organelles [29].

We conclude that statin therapy can be associated with high blood lactate/pyruvate ratios suggestive of mitochondrial dysfunction. Low serum levels of ubiquinone were also observed, but it is uncertain to what extent this feature could explain the mitochondrial dysfunction. We believe that mitochondrial function could be usefully assessed in patients with muscular complications of statin therapy.

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